newly added Claims 27-52 can be found in the specification, for example, on page 8, lines 10-12; page 13, lines 4-5; pages 25, line 27 - page 27, line 2.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the Supplemental IDS is respectfully requested.

Rejection of Claims 1-15, 20-22 and 26 under 35 U.S.C. §112, first paragraph

Claims 1-15, 20-22 and newly presented 26 are rejected under 35 U.S.C. §112, first paragraph for reasons of record. In response to Applicants' statements in the previously filed Amendment mailed to the Patent Office on September 20, 1999, the Examiner states that "evidence and reasoning as to why applicant's working examples are not correlatable to the claimed invention" has been provided (Office Action, page 3). The Examiner states that this aspect of the rejection can be overcome by deleting the phrase "for introducing DNA into an eukaryotic cell, the vector" in Claims 1 and 9.

Claims 1 and 9 have been amended to delete the phrase "for introducing DNA into an eukaryotic cell, the vector".

The Examiner further states that "the claimed genus encompasses any peptide which has an anti-microbial antiviral, or anti-tumor effect" which encompass "antigenic epitopes of viruses, cytokines, perhaps even antisense, none of which are discussed within the specification" (Office Action, page 4). The Examiner also states that "it is not clear how a tumor fits within this class since a tumor is not actually a microbe" (Office Action, page 4). It is the Examiner's opinion that the "specification discloses the genus, lytic peptides, not anti-microbial peptides" (Office Action, page 4).

Applicants respectfully disagree. The claimed genus encompasses any *antimicrobial peptide*, not any peptide, which has an anti-microbial, antiviral, or anti-tumor effect. As indicated in the previously filed Amendment A, the phrase "antimicrobial peptide" is a term of art defined in the scientific literature (see, for example, Bowman and Nikol *et al.* (Exhibit A)). It is also well known in the art that the causative agents of some cancers are viruses (*e.g.*, human papilloma virus and cervical cancer). Applicants maintain that the Examiner has not met her burden of providing acceptable evidence to show that Applicants have not provided an enabling disclosure for the full scope of the claimed invention. As discussed in the previously filed

Amendment A, Applicants have provided working examples demonstrating that administration of a retroviral vector comprising a sequence which codes for antimicrobial peptides (*e.g.*, melittin or cecropin) produces anti-tumor effects *in vivo* and anti-retroviral effects *in vitro*.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 16-19 and 23-25 under 35 U.S.C. §112, first paragraph

Claims 16-19 and 23-25 are rejected under 35 U.S.C. §112, first paragraph for reasons of record. The Examiner states that the "claims are not enabled for use *in vivo*" (Office Action, page 4). It is the Examiner's opinion that the Bowman reference cited in support of the enablement rejection in the previous Office Action mailed from the U.S. Patent Office on March 18, 1999, "provides clear support that the state of the art of using lytic peptides for therapy *in vivo* is unpredictable and not an established art" (Office Action, page 5).

Applicants respectfully disagree. As discussed above, Applicants maintain that the Examiner has not met her burden of providing acceptable evidence to show that Applicants have not provided an enabling disclosure for the full scope of the claimed invention. As discussed in the previously filed Amendment A, Applicants have provided working examples demonstrating that administration of a retroviral vector comprising a sequence which codes for antimicrobial peptides (*e.g.*, melittin or cecropin) produces anti-tumor effects *in vivo* and anti-retroviral effects *in vitro*. In the previously filed Amendment A, Applicants pointed out that their data is recognized in the art as reasonably correlating to the claimed invention (see, for example, Bowman, page 83) and cited the *Brana* case in support thereof.

In support of the 112 rejection, the Examiner has cited the Orkin *et al.*, Verma *et al.* and Bowman references. Of the three references, only Bowman discusses antimicrobial peptides. Orkin *et al.* and Verma *et al.* discuss obstacles encountered using gene therapy at the clinical level. In response to Applicants' position, the Examiner states that "both Orkin and Verma go much deeper than merely discussing the clinical applications" (Office Action, page 3). It is true that, for example, Orkin *et al.* state that "[s]ignificant problems remain in all basic aspects of gene therapy" (Orkin *et al.*, page 1), such as "gene delivery" (Orkin *et al.*, page 7; Verma *et al.*, page 239, column 3). However, the court has recognized that:

> the context of pharmaceutical inventions, necessarily includes the expectation of further research and development (*In re Brana*, 34 U.S.P.Q.2d 1436, 1442 (CAFC 1995).

The court also recognized that to require testing more suited to review by the FDA would involve costs that

> would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer" (*Id.* At 1443).

Furthermore, Applicants' data shows that the claimed construct was successfully delivered and that the antimicrobial peptide was expressed *in* vitro and *in vivo* in an acceptable animal model, *and* that the antimicrobial produced antitumor and antiretroviral effects.

As pointed out in the previously filed Amendment A, the art of record (*i.e.,* Bowman) confirms Applicants' findings. The Examiner notes that Bowman teaches that "the dose given would be critical", however, this is true with most therapeutic interventions. Determination of dosage, although critical, is a routine skill to those in the art. The Examiner also notes that none of the claims are limited to cecropin. However, Applicants have provided two examples (*e.g.,* cecropin and mellitin) of anti-microbial peptides which function in the claimed invention. Where in the art cited is the evidence that other antimicrobial peptides will *not* function as asserted by Applicants in the instant specification?

Even if the Examiner has met her burden of providing acceptable evidence, Applicants have overcome the rejection with suitable proof that the teaching contained in the specification is enabling. The Nikol *et al., Gene Ther., 6(5):*737-748 (May 1999) reference, which is being filed concurrently herewith as Exhibit A, provides further evidence that Applicants have provided an enabling disclosure. Nikol *et al.* refer to Applicants' subsequent publication of the work described in the instant specification (see Nikol *et al.*, page 740, column 2, wherein reference 17 is cited). Reference 17 (*i.e.,* Winder, D., *et al., Biochem. Biophys. Res. Comm., 242:*608-612 (1998)) is being provided herein as Exhibit B for the Examiner's convenience. Using a porcine model, Nikol *et al.* teach that Applicants' retroviral construct carrying the gene encoding the antimicrobial peptide pre-procecropin A, reduced neointima formation *in vivo* and inhibited proliferation (Nikol *et al.*, page 740, column 2; Figure 11). Based on their findings, Nikol *et al.* conclude that "*In vivo* gene transfer of cecropins may be of therapeutic relevance" (Nikol *et al.*, abstract).

Clearly, those of skill in the art would accept Applicants' *in vivo* and *in vitro* data as reasonably correlating to the use of the claimed retroviral vectors for introducing nucleotide sequences into a mammal and/or treating an individual having at least one disease selected from the group consisting of: tumors, viral infections, bacterial infections, fungal infections.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 1-26 under 35 U.S.C. §112, second paragraph

Claims 1-26 are rejected under 35 U.S.C. §112, second paragraph for reasons of record. The Examiner states that although Applicants have defined the term "derivative" as biologically active in Claims 1, 2, 9, 23 and 25, the amendment does not add any definition to the term and the metes and bounds of the claims "remain unclear" (Office Action, page 5). The Examiner states that "derivative" means derived from and therefore, "any peptide which has been derived from the recited peptides is encompassed even if every amino acid in the sequence has been substituted or deleted" (Office Action, page 5). The Examiner concludes that it is impossible to define the metes and bounds of the claimed invention.

Applicants' claimed invention has been amended to further define the biologically active derivative of the therapeutic antimicrobial peptide as "a part, analogue or homologue of the antimicrobial peptide". As indicated above, support for the claimed invention can be found in the specification in original Claim 3, for example. The metes and bounds of the amended claims are now clearly defined.

The Examiner states that the phrase "anti-microbial peptide" in Claims 1, 2, 9 and 23 "would be taken to mean any peptide that would target a microbe by the skilled artisan" (Office Action, page 6). The Examiner further states that "[i]t is not clear that the skilled artisan would accept Bowman's definition because even Bowman uses the term as describing a class of antibiotics" (Office Action, page 6).

Applicants respectfully disagree. As indicated in the previously filed Amendment A and above, the phrase "antimicrobial peptide" is a term of art defined in the scientific literature (see, for example, Bowman and Nikol *et al.* (Exhibit A)). The Examiner cited Bowman as representing those of skill in the art in support of the 112, first paragraph rejection. Clearly, a person of skill in the art would accept Bowman's definition of microbial peptide. Applicants are confused as to the Examiner's reason that one of skill in the art would not accept the Bowman definition "because even Bowman uses the term as describing a class of antibiotics" (Office Action, page 6. Bowman clearly states that the "animal peptide antibiotics discussed here are all gene encoded and made from an RNA template read by ribosomes" (Bowman, page 62). The

Bowman reference provides clear evidence that a person of skill in the art is clearly apprized of the term "antimicrobial peptide".

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No. 40,564
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799
Dated: November 22, 2000